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Evaluation of Cardiac Arrhythmia Susceptibility in Pediatric Familial Mediterranean Fever Patients

Pediatrik Ailevi Akdeniz Ateşi Hastalarında Kardiyak Aritmi Yatkınlığının Değerlendirilmesi

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Abstract

Aim: Familial Mediterranean fever is an autoinflammatory disease characterized by attacks of inflammation. Despite treatment, there is evidence of subclinical persistence of inflammation with normal laboratory values. This study was conducted to investigate the cardiac effects of continued subclinical inflammation in children and the predisposition towards arrhythmia in familial Mediterranean fever.

Material and Method: Age and sex-matched familial Mediterranean fever patients and healthy controls were compared in terms of demographic, laboratory, echocardiographic and electrocardiographic data. The patients with familial Mediterranean fever were grouped according to disease severity scores and compared in terms of electrocardiographic data that could indicate arrhythmogenesis. Correlation analysis was used to examine the relationship between the electrocardiographic measurements and the clinical and laboratory data.

Results: In the comparison of the two groups, no significant difference was found in the echocardiographic measurements in terms of left ventricular systolic and diastolic functions. According to these data, QT and Tp-e intervals were significantly longer in those with familial Mediterranean fever (p=0.002, p=0.046, respectively). When the patients were classified according to the 3 separate disease severity scores, QT dispersion in the moderate-severe disease group was significantly longer than in the mild disease group (p<0.001, p=0.002, p=0.013, respectively). In correlation analysis, weak correlations were found between and QT dispersion, disease duration and P wave dispersion, and frequency of attacks and QT dispersion.

Conclusion: Our study results indicate that the predisposition to ventricular arrhythmia is greater in children with familial Mediterranean fever and that this can be associated with the severity of the disease.

Keywords: Arrhythmia, electrocardiography, familial Mediterranean fever

Öz

Amaç: Ailevi Akdeniz ateşi inflamasyon atakları ile karakterize otoinflamatuar bir hastalıktır. Tedaviye rağmen, normal laboratuvar değerleri ile subklinik inflamasyonun devam ettiğine dair kanıtlar vardır. Bu çalışma, çocuklarda devam eden subklinik inflamasyonun kardiyak etkilerini ve ailevi Akdeniz ateşinde aritmiye yatkınlığı araştırmak için yapılmıştır.

Gereç ve Yöntem: Yaş ve cinsiyet açısından eşleştirilmiş ailevi Akdeniz ateşi hastaları ve sağlıklı kontroller demografik, laboratuvar, ekokardiyografik ve elektrokardiyografik veriler açısından karşılaştırıldı. Ailevi Akdeniz ateşi hastaları hastalık şiddeti skorlarına göre gruplandırıldı ve aritmogenezi gösterebilecek elektrokardiyografik veriler açısından karşılaştırıldı. Elektrokardiyografik ölçümler ile klinik ve laboratuvar verileri arasındaki ilişkiyi incelemek için korelasyon analizi kullanıldı.

Bulgular: İki grup karşılaştırıldığında, ekokardiyografik ölçümlerde sol ventrikül sistolik ve diyastolik fonksiyonları açısından anlamlı bir fark bulunmadı. Bu verilere göre QT ve Tp-e intervalleri ailesel Akdeniz ateşi olanlarda anlamlı olarak daha uzundu (sırasıyla p=0.002, p=0.046). Hastalar 3 ayrı hastalık şiddeti skoruna göre sınıflandırıldığında, orta-şiddetli hastalık grubunda QT dispersiyonu hafif hastalık grubuna göre anlamlı olarak daha uzundu (sırasıyla p<0.001, p=0.002, p=0.013). Korelasyon analizinde, QT dispersiyonu ile QT dispersiyonu, hastalık süresi ile P dalga dispersiyonu ve atak sıklığı ile QT dispersiyonu arasında zayıf korelasyonlar bulunmuştur.

Sonuç: Çalışma sonuçlarımız ailevi Akdeniz ateşi olan çocuklarda ventriküler aritmiye yatkınlığın daha fazla olduğunu ve bunun hastalığın şiddeti ile ilişkili olabileceğini göstermektedir.

Anahtar Kelimeler: Aritmi, elektrokardiyografi, ailevi Akdeniz ateşi

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INTRODUCTION

Familial Mediterranean fever (FMF) is an inherited autosomal recessive disorder and the most common monogenic and autoinflammatory disease that is characterized by recurrent and self-limited attacks of polyserositis.[1] It is believed that the disease is caused by mutations in the MEFV gene that encodes pyrin protein on the short arm of chromosome 16. The mutated pyrin activates pyrin inflammasome, causing the uncontrolled secretion of cytokines that leads to inflammation.[2] There is evidence suggesting that patients with FMF have continued subclinical inflammation even in periods when they are not experiencing attacks.[3] Chronic inflammation and its sequels can cause anemia and splenomegaly, continuously high acute phase reactants, and the most feared complication of amyloidosis.[2]

Cardiovascular system involvement is among the causes of high morbidity and mortality in FMF. While FMF-related pericarditis and cardiac amyloidosis are the most commonly expected complications, recent studies have reported that FMF patients can suffer sudden cardiac death or malign arrhythmias that are caused by cardiac repolarization abnormalities, even without the presence of amyloidosis.[4,5] This has been linked to the chronic inflammation occurring in FMF. It is believed that the chronic inflammation observed in FMF can lead to endothelial injury and ischemic cardiovascular damage.[6-9] It is considered that this condition can occur not only during periods of attack but also in patients who do not experience attack.[10,11]

There are various parameters that indicate myocardial repolarization in an electrocardiogram. The abnormalities in these parameters may foresee a tendency toward arrhyrthmia. The most commonly known of these are the T wave, Tp-e interval, corrected Tp-e interval, the QT interval, corrected QT interval, Q wave dispersion, P wave dispersion. It has been found that prolonged Tp-e, corrected QT rates are associated with life-threatening ventricular arrhythmias such as life-threatening polymorphic ventricular tachycardia, torsades de pointes, and ventricular fibrillation.[12,13] There are many studies in the literature which have used these new indices that indicate ventricular repolarization in FMF.[4,5,14-16] Studies have revealed that the Tp-e interval is superior to QT dispersion in foreseeing sudden cardiac death and ventricular arrhythmia.[17]

Our aim in this study was to evaluate the longstanding as well as the newly developed electrocardiogram parameters indicating myocardial repolarization and to assess the QT interval, corrected QT interval, Tp-e interval, corrected Tp-e, Tp-e/corrected QT, P wave dispersion to see whether pediatric patients diagnosed with FMF have a predisposition toward arrhythmia.

MATERIAL AND METHOD

Study Population

Between September 2017 and September 2019, 44 pediatric patients aged <18 years who were treated with a diagnosis of FMF in our Pediatric Rheumatology unit were included in the study. FMF was diagnosed according to the diagnostic criteria proposed by Yalçınkaya and Özen.[18] Those with congenital or acquired heart disease, problems in cardiac conduction, electrolyte imbalance, those who have had an attack in the last 3 months, smokers, those with concomitant diseases (diabetes, hypertension, hypothyroidism, anemia, obesity, chronic kidney disease, chronic lung disease, etc.) and those who were not followed up regularly were excluded from the study.

The control group consisted of 44 children who were of the same age and gender as those patients with FMF, had no chronic disease, who had presented to the pediatric cardiology outpatient clinic for an innocent heart murmur or for a health report needed for participating in sports, or who had presented to the pediatric rheumatology outpatient clinic for growth pains.

The patients and the control group were matched one-to-one in terms of age and gender. There was no difference between the two groups in terms of body mass index.

Study Design

The blood pressure of the patients and the control group was taken. Blood samples were drawn for a complete blood count, glucose, creatinine, electrolyte and albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urinalysis, and thyroid function tests. Electrocardiography and transthoracic echocardiography were taken. Body mass index was calculated by dividing body weight (kilograms) by height squared (meters). C-reactive protein was assessed by nephelometric and ESR Westergreen methods. Laboratory devices that were regularly monitored for accuracy and calibration were used for the biochemistry tests and complete blood count.

The laboratory and cardiac investigations of the patients were evaluated for a period of at least 3 months in which there were no attacks.

Also, the patients were divided into three groups according to their disease severity scores–mild, moderate and severe. Pras et al.'s scoring system[19], Mor et al.'s scoring system[20], and the International Severity Score for Familial Mediterranean Fever (ISSF)[21] were employed in the scoring. The patients were divided into groups according to these three scoring systems and were assessed to find out whether there were any differences between them in terms of myocardial repolarization parameters.

The local ethics committee approved the study with its decision of 2020/274.

Electrocardiography

An electrocardiogram was taken at 50mm/s speed and 1mV / cm standardization with a 12-lead electrocardiography device after each child had rested for 10 minutes and had been placed in a supine position (Nihon Kohden electrocardiogram, Cardiofax GEM, Model 9022K, Tokyo, Japan). All electrocardiography recordings were transferred to a computer via a scanner, after which Adobe Photoshop software was used for a x400 enlargement. To reduce the margin of error, the measurements were made with an electronic digital caliper. All measurements were taken by two researchers who were blinded to the clinical condition of the patients and controls. An average value of two measurements was calculated for each parameter. Heart rate, rhythm, R-R interval, P wave interval, QT interval, corrected OT interval, QT dispersion, Tp-e interval, corrected Tp-e, Tp-e/corrected QT were calculated.

The QT interval was calculated as from the start of the Q wave to the point where the T wave returned to the isoelectric line, using the corrected QT Modified Bazett formula (corrected QT=QT/√ R-R interval). The Tp-e interval was measured as the distance between the peak and end of the T wave. First a V5 derivation was used for the measurement and when this was not appropriate (concentrated artifacts or T wave amplitude of ≤ 1.5mV), V4 and V6 leads were used respectively. QT dispersion was found by calculating the difference between the longest QT interval at derivation 12 and the shortest QT interval. P wave dispersion was found by calculating the difference between the p wave time calculated to be the longest at derivation 12 and the P wave time calculated to be the shortest. To adjust Tp-e time according to the corrected QT and heart rate defined in the literature, the following formulas were used: Tp-e corrected QT: Tp-e/corrected QT and corrected Tp-e: Tp-e/√R-R. The intra-observer and inter-observer variations for all measurements were <5%, and therefore insignificant.

Transthoracic Echocardiographic Examination

All echocardiographic and Doppler assessments were performed by a single pediatric cardiology expert who was blinded to the clinical and laboratory results of the study group. Epiq 7 echocardiography equipment (Philips Healthcare, Minnesota, United State) with a 3MHz phased-array transducer was used for each subject. The echocardiographic evaluation from the parasternal long-axis view included left ventricular end-diastolic and end-systolic diameters, septum and left ventricular posterior wall thicknesses in diastole and systole, and left ventricular ejection fraction and fractional shortening. Teichholz's M-mode formula was used to calculate left ventricular ejection fraction and fractional shortening. All data were obtained according to the recommendations of the American Society of Echocardiography.[22] The left atrial dimension was measured from the parasternal long-axis window in M-mode echocardiograph.

Statistical Analysis

All data were analyzed with the SPSS 15.0 (SPSS Inc., Chicago, IL, USA) program. Mean±standard deviation was used for numerical variables, and percentages for categorical data. If the numerical data showed normal distribution in the comparison of the data of children with FMF and healthy children, the Student-t test was employed; if the data did not display normal distribution, the Mann Whitney-U test was used. The chi-square test was used in the comparison of categorical data. If the correlational variables between the parameters were normally distributed, Pearson's correlation analysis was used, while Spearman's correlation analysis was employed if they were not normally distributed. A correlation coefficient and p values were obtained. Statistical significance was accepted as $p<0.05$.

RESULTS

Demographic and Clinical Characteristics

Forty-four patients with FMF and 44 healthy children were included in the study. In both groups, there was a total of 25 girls (56.8%) and 19 boys (43.2%). The mean age of the patients was 11.38±4.21 years; that of the control group was 11.61±4.16 years.

The mean age at which FMF started was 6.2±3.4; the duration of the disease was a mean 5.40±3.68 years. The frequency of attacks was at a median of once every 5 months (minimum 3 months, maximum 12 months). The duration of attacks were at a median of 2 (minimum 2-maximum 3) days. The median dose of colchicine taken by the patients was 0.5 mg (minimum 0.25 mg-maximum 2 mg).

In the classification of the patients according to their disease severity scores in line with the scoring system of Pras et al., 9 patients (20.4%) displayed mild, 29 patients (65.9%) showed moderate, and 6 patients (13.6%) severe forms of the disease. According to the scoring system of Mor et al., 23 patients (52.2%) displayed mild, 13 patients (29.5%) showed moderate, and 8 patients (18.1%) severe disease. The ISSF scoring showed that 20 patients (45.4%) exhibited mild, 18 patients (40.9%) moderate, and 6 patients (13.6%) severe disease.

Demographical and clinical characteristics are shown in **Table 1**. Comparison of Laboratory Features

Laboratory findings and comparisons of the patients and the control group can be seen in **Table 1**. Although ESR, potassium, phosphorus, creatinine values were within the reference range in both the FMF group and the controls, a statistically significant difference for each value was detected between the two groups (p values: p=0.038, p=0.019, p=0.019, p=0.04, respectively). While creatinine and potassium were statistically and significantly high in the control group, the patient group displayed high levels of phosphorus and ESR.

Table 1: Demographic, clinical and laboratory characteristics of the pediatric familial Mediterranean fever patients

	FMF patients n=44	Control n=44	p value
Gender			
Male (n, %)	19 (43.2%)	19 (43.2%)	1
Female (n, %)	25 (56.8%)	25 (56.8%)	
Age, mean (SD)	11.38 (4.21)	11.61 (4.16)	0.80
BMI	21.40 (1.32)	22.12 (2.11)	0.64
Clinical Manifestations	**Mean (SD) or Median (min-max)**		
Age at onset (year)	6.20 (3.42)		
Disease duration (year)	5.40 (3.68)		
Attack frequency (month)	5 (3-12)*		
Attack duration (day)	2 (2-3)*		
Dose of colchicines (Tb)	1.00 (0.5-3)		
Severity Scores	**n (%)**		
Pras et al			
Mild	9 (20.5)		
Moderate	29 (65.9)		
Severe	6 (13.6)		
Mor at al			
Mild	23 (52.2)		
Moderate	13 (29.5)		
Severe	8 (18.1)		
ISSF			
Mild	20 (45.4)		
Moderate	18 (40.9)		
Severe	6 (13.6)		
Laboratory features	**Mean (SD) or Median (min-max)**	**Mean (SD) or Median (min-max)**	**p value**
CRP	1.44 (1.09-2.64)*	1.52 (1.25-2.32)*	0.34†
ESR	6 (3-13)	4 (2-9)	0.038†
Wbc	7.27 (2.17)	7.14 (2.31)	0.79
Hb	13.23 (1.33)	13.45 (1.35)	0.45
Plt	313.00 (74.79)	296.50 (67.58)	0.29
Neuthrophil	8.28 (1.03)	3.75 (2.13)	0.71
Na	138.90 (1.84)	138.71 (2.32)	0.68
K	4.30 (0.29)	4.46 (0.33)	0.019
Cl	104 (103-105)*	104 (103-105)*	0.37†
Ca	9.9 (9.6-10.2)*	9.9 (9.7-10.1)*	0.99†
P	4.75 (0.51)	4.45 (0.63)	0.019
Mg	2.02 (0.13)	2.03 (0.15)	0.76
Albumine	4.45 (4.30-4.60)*	4.40 (4.30-4.60)*	0.44†
Creatinine	0.49 (0.14)	0.59 (0.15)	0.004

FMF: Familial Mediterranean fever, SD: Standart deviation, Min: minimum, Max: maximum, BMI: Body mass index, Tb: Tablet, ISSF: International severity score of Familial Mediterranean Fever, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Wbc: White blood cell, Hb: Hemoglobulin, Plt: Platelet, Na: Sodium, K: Potassium, Cl: Chlorine, Ca: Calcium, P: Phosphorus, Mg: Magnesium
*Non-normally distributed values
† Mann-Whitney -U test, p<0.05 is statistically significant

Comparison of Cardiovascular Parameters

No difference was found between the FMF and control groups in terms of heart rate, systolic-diastolic blood pressure and echocardiographic parameters. The RR, QT and Tp-e intervals were statistically and significantly higher in the patient group compared to the controls (p values: p=0.020, p=0.002, p=0.046, respectively). A comparison of cardiovascular parameters can be found in **Table 2**.

Table 2: Comparison between cardiovascular, electrocardiographic and echocardiographic measurements of patients and controls

	FMF	Control	p value
Blood pressures	Mean (SD)	Mean (SD)	
Systolic blood pressure (mmHg)	106.15 (11.93)	100 (0.0)	0.49
Diastolic blood pressure (mmHg)	58.08 (8.30)	60 (0.0)	0.76
Electrocardiographic measurements	**Mean (SD)**	**Mean (SD)**	
Hearth rate (beat/min)	88.34 (13.78)	83.74 (12.76)	0.11
RR interval (msec)	486.05 (122.59)	435.07 (70.35)	0.020
QT interval (msec)	235.98 (50.81)	208.49 (22.99)	0.002
QTc interval (msec)	340.98 (45.29)	324.12 (41.36)	0.074
QT dispersion(msec)	36.64 (16.12)	35.30 (12.45)	0.67
Tp-e interval (msec)	52.84 (15.12)	47.37 (9.31)	0.046
cTp-e interval (msec)	2.39 (0.56)	2.29 (0.48)	0.34
Tp-e/QTc (ratio)	0.15 (0.03)	0.15 (0.03)	0.33
P dispersion (msec)	23.18 (6.69)	25.58 (10.93)	0.22
Echocardiographic measurements	**Mean (SD)**	**Mean (SD)**	
EF (%)	68.98 (4.80)	68.15 (4.08)	0.39
FS (%)	37.59 (3.80)	36.43 (5.47)	0.25
IVSd thickness (mm)	7.40 (1.19)	7.13 (1.33)	0.31
IVSs thickness (mm)	8.69 (1.37)	9.83 (9.78)	0.44
LVEDd (mm)	35.33 (3.98)	43.51 (47.47)	0.26
LVEDs (mm)	22.01 (3.26)	22.44 (4.08)	0.59
LA dimension (mm)	22.03 (2.72)	21.49 (5.11)	0.56
LVPWd (mm)	7.38 (1.42)	7.43 (2.13)	0.89
LVPWS (mm)	9.43 (2.39)	9.65 (2.27)	0.65
Aorta diameter (mm)	19.63 (2.87)	19.57 (3.96)	0.95
Mitral E (m/s)	0.90 (0.08)	1.48 (3.20)	0.28
Mitral A (m/s)	0.61 (0.10)	1.74 (6.69)	0.28
E/A ratio	1.51 (0.25)	1.55 (0.39)	0.62

SD: Standart deviation, EF: LV ejection fraction, FS: LV fractional shortening, IVSd: Interventricular septal diameter in diastole, IVSs: Interventricular septal diameter in systole, LVEDd: LV end-diastolic diameter, LVEDs: LV end-systolic diameter, LVPWd : LV posterior wall diameter in diastole, LVPWS: LV posterior wall diameter in systole, LA: Left atrial dimention, Aort: Aortic dimension, mitralE: Mitral peak early diastolic wave (E), mitralA: Mitral peak late diastolic wave (A), EA: Mitral peak early diastolic wave/peak late diastolic wave ratio, p<0.05 is statistically significant

Correlation between Patients' Electrocardiography Parameters and Clinical Features

A weak positive correlation was found between disease duration and P wave dispersion (p=0.039, correlation coefficient=0.331). A weak correlation was found between attack frequency and QT dispersion (p=0.032, correlation coefficient=-0.345), while a weak negative correlation was found between attack duration and RR and QT intervals (p=0.003, correlation coefficient=-0.461; p=0.019, correlation coefficient=-0.365, respectively). There was also a weak positive correlation between ESR and QT dispersion (p=0.030, correlation coefficient=0.240) (**Table 3**).

The Relationship Between Disease Severity and Electrocardiography Parameters

Since the size of the patient group was small, the groups were classified as mild and moderate-severe in all three scoring systems. When evaluated in this way, it was found that according to all three scoring systems, QT dispersion was longer in the group with moderate-severe disease compared to the group with mild disease (p<0.001, p=0.002, p=0.013, respectively). The correlation between disease severity scores and electrocardiograph data is reviewed in **Table 4**.

Table 3: Correlation between electrocardiography parameters of the patients and their clinical/laboratory features

Clinical features	RR interval	QT interval	QT dispersion	QTc interval	Tpe interval	cTpe interval	Tpe/QTc ratio	P wave dispersion
Age at disease onset								
Coefficient corelation	0.139	0.113	-0.039	0.006	0.15	0.105	0.161	-0.065
p value	0.400	0.492	0.814	0.973	0.363	0.524	0.327	0.695
Disease duration								
Coefficient corelation	0.287	0.186	0.054	0.028	0.085	-0.013	0.151	0.331
p value	0.076	0.256	0.745	0.868	0.609	0.94	0.36	0.039
Attack frequency								
Coefficient corelation	0.007	-0.041	0.345	-0.059	-0.016	-0.01	-0.041	-0.078
p value	0.968	0.805	0.032	0.721	0.922	0.953	0.803	0.635
Attack duration								
Coefficient corelation	-0.461	-0.375	-0.024	-0.216	-0.282	-0.196	-0.411	-0.057
p value	0.003	0.019	0.882	0.187	0.082	0.233	0.090	0.729
ESR								
Coefficient corelation	-0.078	0.063	0.240	0.091	-0.25	0.00	-0.115	0.093
p vavlue	0.484	0.571	0.030	0.416	0.824	0.999	0.303	0.405
K								
Coefficient corelation	0.039	-0.66	0.024	-0.164	-0.081	-0.107	0.053	-0.043
p value	0.726	0.549	0.825	0.136	0.464	0.333	0.634	0.638
P								
Coefficient corelation	0.010	0.159	0.141	0.153	0.081	0.078	-0.017	-0.180
p value	0.932	0.153	0.208	0.175	0.571	0.487	0.877	0.106
Cre								
Coefficient corelation	0.184	-0.050	0.131	-0.119	-0.074	-0.162	-0.025	0.201
p value	0.096	0.654	0.239	0.285	0.505	0.144	0.815	0.069

K: Potassium, P: Phosphorus, Cre: Creatinin, ESR: Erythrocyte sedimentation rate, QTc: Corrected QT, cTp-e: Corrected Tp-e, p<0.05 is statistically significant

Table 4: Comparison of electrocardiographic measurements among familial Mediterranean fever patients according to disease severity scores

Electrocardiographic measurements	Pras et al severity score		p value
	Mild (n=9) Mean (SD)	Moderate-Severe (n=35) Mean (SD)	
RR interval	90.78 (13.16)	93.29 (17.22)	0.74
QT interval	208.49 (22.99)	235.17 (51.93)	0.84
QTc interval	343.11 (35.50)	340.43 (47.92)	0.88
QT dispersion	32.40 (9.41)	53.11 (25.23)	<0.001
Tpe interval	50.44 (13.61)	53.46 (15.61)	0.60
cTpe interval	2.27 (0.42)	2.43 (0.60)	0.46
Tpe/QTc ratio	0.15 (0.04)	0.15 (0.03)	0.56
P dispersion	25.44 (6.58)	22.60 (6.69)	0.26
	Mor et al severity score		
	Mild (n=23) Mean (SD)	Moderate-Severe (n= 21) Mean (SD)	p value
RR interval	516.43 (128.67)	482.94 (113.62)	0.08
QT interval	244.52 (49.24)	226.62 (52.03)	0.25
QTc interval	345.09 (40.67)	336.48 (50.51)	0.54
QT dispersion	29.19 (6.70)	43.43 (19.12)	0.002
Tpe interval	55.52 (14.92)	49.90 (15.14)	0.22
cTpe interval	2.45 (0.57)	2.33 (0.56)	0.50
Tpe/QTc ratio	0.16 (0.03)	0.15 (0.03)	0.33
P dispersion	24.39 (7.01)	21.86 (6.22)	0.21
	ISSF		
	Mild (n=20) Mean (SD)	Moderate-Severe (n=24) Mean (SD)	p value
RR interval	501.40 (137.54)	473.25 (109.98)	0.45
QT interval	237.10 (51.42)	235.04 (51.39)	0.90
QTc interval	340.35 (41.07)	341.50 (49.41)	0.93
QT dispersion	31.25 (8.66)	43.10 (20.41)	0.013
Tp-e interval	53.10 (15.64)	52.63 (15.01)	0.92
cTp-e interval	2.37 (0.59)	2.41 (0.55)	0.83
Tpe/QTc ratio	0.15 (0.03)	0.15 (0.03)	0.75
P dispersion	24.15 (6.96)	22.38 (6.50)	0.39

ISSF: International severity score of familial Mediterranean fever, QTc: Corrected QT, cTp-e: Corrected Tp-e, SD: Standart deviation, p<0.05 is statistically significant

DISCUSSION

We found in our study that RR, QT and Tp-e intervals were significantly longer in FMF patients. Since prolongations in these parameters on the electrocardiography could be related to ventricular arrhythmia, we considered that FMF patients may have increased cardiac arrhythmia risk compared to the control group. We examined the correlation between ESR and the cardiac repolarization parameters of QT and Tp-e. We could not find any correlation between ESR and these parameters, but we did detect a weak correlation with QT dispersion. We also found that QT dispersion duration was significantly longer in the group with moderate and severe disease compared to those with mild disease. In many studies, QT dispersion has been found to be associated with cardiac arrhythmias.[23,24] In our study, the fact that the QT and Tpe intervals were longer in the FMF group compared to the controls, and that the prolongation of the QT dispersion was also associated with the severity of the disease suggested that subclinical inflammation predisposes to ventricular arrhythmia in patients with FMF.

Familial Mediterranean fever is a disease that is characterized by recurrent attacks of inflammation.[25] Controlling inflammation is the most effective way of preventing the mortality and morbidity caused by the disease. Despite this, however, some studies have shown that the effects of FMF persist even in the absence of inflammation.[26,27] Many markers have been studied, especially in hemograms, in order to detect subclinical inflammation, but as yet no clear conclusions have been drawn.[28,29] It was interesting to note that although ESR values were in the normal range in both our patients and in the control group, these values were significantly higher in the FMF group. This may be discussed as an indication of subclinical inflammation, but this is not the aim of our study.

It has been shown that continued subclinical inflammation leads to endothelial dysfunction in the heart muscle and that endothelial dysfunction leads to vasculitis and in turn, to ischemia-related focal fibroses.[30-33] In our study, no difference was detected between the patients with FMF and the healthy controls in terms of echocardiographic measurements, left ventricular systolic and diastolic functions. Since we worked with pediatric patients in our study, we considered that the duration of the disease may not be enough to spot potential changes in coronary microvascular circulation.

Cardiac arrhythmia is a serious condition that can result in sudden death. It is thought that transmission problems and rhythm disorders are associated with continued inflammation-related ischemia and/or local fibrosis in FMF.[15,34] The myocardial repolarization QT duration, QT dispersion and transmural repolarization can be calculated and evaluated.[35-37] While the peak point of the T wave on the electrocardiography signifies the end of the epicardial action potential and the earliest completed repolarization on the ventricular wall, the end of the T wave corresponds to the end of the mid myocardial action potential; this distance is thought to indicate total repolarization.[13] It is therefore believed that Tp-e reflects transmural repolarization distribution. Furthermore, because the Tp-e/ corrected QT ratio is not affected by dynamic changes in heart rate in terms of indicating ventricular repolarization and arrhythmogenesis, it is believed it is more sensitive to indicating ventricular repolarization.[38] Yamaguchi et al. have observed that the Tp-e interval is more valuable than QT dispersion in terms of predicting torsades de pointes in patients with acquired long QT syndrome.[39] It has been noted in other studies that the Tp-e interval is prolonged in diseases such as rheumatoid arthritis, systemic lupus erythematosus.[40,41] Studies with adult patients have shown that the Tp-e interval and corrected Tp-e/QT ratio is statistically and significantly prolonged compared to healthy controls in FMF.[14,15] In our study, we observed that the QT and Tp-e intervals displaying ventricular repolarization in the FMF group were significantly more prolonged than in the control group.

QT dispersion is an index that is newly being introduced as a measure of arrhythmogenicity.[42] Akçay found increased QT dispersion in individuals with FMF compared to healthy controls.[4] On the other hand, there are also studies that have not indicated any significant difference between FMF and healthy groups in terms of QT dispersion.[32,33] In pediatric cases, Fidancı et al. reported increased QT dispersion in pediatric FMF patients compared to healthy controls.[16] In a study by Koca et al., the authors did not find a difference between FMF and control groups in terms of QT dispersion and corrected QT dispersion.[43]

The increase in P wave dispersion is correlated with heterogeneity in atrial transmission and it is assumed that this is a risk for atrial fibrillation and relapse.[44,45] In the present study, we found a positive and weak correlation between P wave dispersion and disease duration. On the other hand, no difference was found between the FMF group and the healthy controls in terms of P wave dispersion.

Differing from other studies, our research included the evaluation of electrocardiographic parameters in terms of patients' disease severity scores. For a more accurate statistical analysis, the patients were divided into two groups of mild and moderate-severe and according to all 3 scoring systems, QT dispersion was seen to be significantly longer in the moderate-severe group compared to the group with mild disease. QT dispersion's sensitivity in determining arrhythmogenesis and the fact that similar results were found in all 3 scoring systems suggests that even though there may be no apparent sign of inflammation in FMF, the subclinical inflammation occurring as disease severity progresses will increase arrhythmogenesis.

The present study had some limitations, the most important of which was that the sampling consisted solely of pediatric patients and the number of patients was limited. Another limitation was that because the follow-up periods had to be made at short intervals due to the younger ages of the individuals, it was not possible to work with definitive data. We believe it will be of much more benefit from a scientific point of view if this type of study can be carried on into the children's adult phase so that 5- and 10-year comparisons can be made.

CONCLUSION

In conclusion, the adverse effects of inflammation on transmission systems are known. We detected significant changes in our study in individuals with FMF compared to the healthy controls, noting that moderate-severe FMF disease showed more significant changes in terms of predicting arrhythmogensis than in individuals with mild disease. This led us to think that subclinical inflammation in FMF can be the cause of ventricular arrhythmias. The correlation between the increase in the severity of the disease and the widening of QT dispersion reinforced our thesis. We believe that studies with longer follow-ups and larger patient populations will enable the collection of more accurate results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University local ethics committee (Decision No: 2020/274).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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